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# A New Pharmacoscintigraphic Technique for the Evalution of Pharmacokinetic Processes

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## ABSTRACT

In last few years for developing new chemical moiety or drug more time and more money is required. Also more energy is required to investigate the new molecule and to study its in-vitro analysis. A lot of time is been invested in study of pharmacokinetic parameters in the body. It includes study of absorption, distribution, metabolisam and excerition. Dissolution study is important for in-vitro analysis of data or release of drug in the formulation and by using blood sampling and urine analysis in-vivo study is carried out. But this method requires much more time for analyzing data. Now we can save our time, money and energy by using a new pharmacoscintigraphic technique. A pharmacokinetic and pharmacodynamic study of newly investigated drug is carried out by using pharmacoscintigraphic technique. If any dosage form is administered by the body by any intended route then this body is scanned under gamma cameras and thus it can give whole information about rate,extent,site and mode of drug release. A new drug delivery systems are also evaluated by pharmacoscintigraphic technique.
**Keywords:** Pharmacokinetic study, *in-vitro*, *in-vivo* analysis, pharmacoscintigraphy

## I. INTRODUCTION

In last few years for developing new chemical moiety or drug more time and more money is required. Also more energy is required to investigate the new molecule and to study its in-vitro analysis. A lot of time is been invested in study of pharmacokinetic parameters in the body.[1]

Pharmacoscintigraphic, the application of Nuclear Medicine in drug development is a recent advancement. The safety, reproducibility, quantification and sensitivity of scintigraphy to detect pharmacological perturbation, together with wide choice of radiopharmaceuticals and flexibility of imaging procedures makes it an ideal modality to evaluate drugs / drug formulations.In India, a formal beginning of pharmacoscintigraphy has now been made at INMAS, DRDO, Delhi. Though presently its commercial use is limited, the scope is immense. Major advantages include high throughput screening at pre-clinical stage, objective *zero-phase* human trials and reduced size of other phases of clinical trial leading to significant reduction in developmental cost and time, and evidence based comparison of the test drug / formulation with the conventional products in vitro, in animals and in humans.

Pharmacokinetic simulation models can be designed based on the information about the physiological environments around the delivery system and knowledge of its transit parameters in the GI tract (Grass and Sinko, 2002). The most convenient way to obtain the required in vivo transit data for the model is conducting an imaging study of the delivery system simultaneously with a common pharmacokinetic study. These kinds of studies are referred to as ‘pharmaco-scintigraphy’. The combined data enables modelling of the dosage form behaviour and systemic pharmacokinetics of the drug simultaneously. Such physiologically-based models are useful in the analysis of the roles of the physiological factors and formulation parameters on inter-individual variance. Furthermore, they are useful in predicting in vivo behaviour of modified drug delivery systems. Implementation of scintigraphy-based pharmacokinetic modelling in the drug development processes may

reduce the rate of product attrition in the expensive clinical drug development phases.

**Gamma Scintigraphy**

The first applied studies of gamma scintigraphy in the context of per oral pharmaceutical dosage forms were carried out in the 1970's (Casey et al., 1976; Alpsten et al., 1976). The technique had already been used for many years in studying the physiology of gastrointestinal (GI) tract (Griffiths et al., 1966). The idea was originally to gain information in relation to the anatomy and the physiology of the human body by using radio nuclides that localize in specific organs. When using high enough activity levels, also radiotherapy for treatment of e.g. tumours became possible. Soon after, it was discovered that the same basic procedure can be utilized in drug studies. Pharmaceutical gamma scintigraphy takes a step forward beyond the traditional anatomical imaging because the movements of drug molecules or delivery systems are monitored continuously. Therefore, it is called functional imaging.

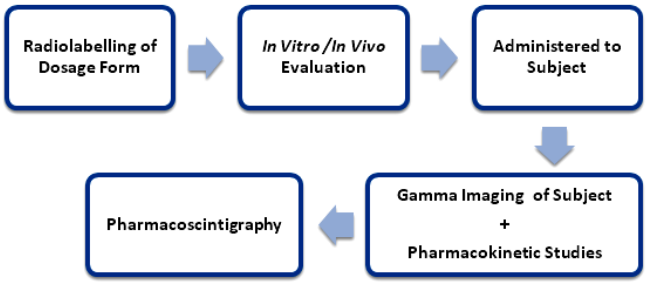


**Figure 1:** Fundamental principle of pharmacoscintigraphy

**Methods of Radiolabelling**[2]

The use of compounds labelled with radionuclides has grown considerably in medical, biomedical and other related fields. In radiolabelled compounds, atoms or groups of atoms of a molecule are substituted by similar or different radioactive atoms or groups of atoms. In radiolabeling process, a variety of physicochemical conditions can be employed to achieve a specific kind of labelling. There are six major methods employed in the preparation of labelled compounds for clinical use:

1. Isotope exchange
2. Introduction of a foreign label
3. Labelling with bi-functional chelates
4. Biosynthesis
5. Recoil Labelling
6. Excitation labelling.

**Uses of pharmacoscintigraphy** (3)

1. Formulation development & quality control
2. In vitro data generation
3. 3.Animal & human pharmacokinetic & pharmacodynamic data
4. 4.Formulation imaging

## II. METHODS AND MATERIAL

Gamma scintigraphy is an imaging technique that enables the direct visualisation and quantification of events occurring in vivo, in real time. Initially introduced as diagnostic tool, the potential of this method was quickly realised within the pharmaceutical industry. Gamma scintigraphy was first reported for the measurement of transit times in 1966 (gastric emptying) followed swiftly by the assessment of drug product performance in 1976 (capsule disintegration) 4, 5.Visualisation is achieved by the incorporation of short half-life gamma emitting radionuclides, eg technetium-99m (99mTc) and indium-111 (111In). The chosen radionuclide(s) is used to label the drug product or, for pharmacodynamic investigations, the component of interest (eg food or fluid for gastrointestinal transit; inhaled particles for mucociliary clearance). The radiation dose to the subject is minimal – often not exceeding that received from a single X-ray. A gamma camera is used to detect the gamma rays and record these as primary counts which are represented as an image (Figure 1).

Gamma scintigraphic investigations can be routinely incorporated into standard phase 1/2a studies alongside safety, pharmacokinetic and other biomarker assessments.

## III. APPLICATIONS IN DRUG PRODUCT DEVELOPMENT

### A. Oral products

The production of an oral product starts in the laboratory, where the pharmaceutical scientist is charged with developing a dosage form which meets a pre-determined specification for drug release. Release rate is measured by recognised methods, for example dissolution testing coupled with HPLC, to generate a

profile of drug release versus time. The primary use of these data is for the comparison/differentiation of prototype formulations, and for quality control. However, the results are also often intended as a representation of formulation performance in simulated in vivo conditions and are used as a first stage tool for formulation selection. However, an in vitro method cannot take into account all of the physiological factors that influence formulation performance and even if an in vitro-in vivo correlation (IVIVC) can be established, this is only confirmed after completion of a clinical study. Clinical studies designed to assess the performance of prototype formulations generate pharmacokinetic parameters. These data are at least onestep removed from formulation performance and so, when the pharmacokinetic profile is not as predicted, educated guesswork is needed to determine – and more importantly, fix – the cause.

Scintigraphic data provide the missing information, offering real-time visualisation and measurement of in vivo formulation performance. Key data are the rate of erosion of the dosage form – equating to release of drug (Case study 1)[6]. These data correspond to those obtained from in vitro dissolution, and assuming no other rate limiting factors may also parallel the appearance of drug in the systemic circulation. A further level of detail is obtained by tracking the transit of the dosage form through the gastrointestinal tract. How long does a gastroretentive formulation remain in the stomach? To which regions does an extended release formulation deliver? How rapidly does an enteric coated formulation deliver drug after gastric emptying? Does a colon targeting formulation reproducibly deliver to the target site?[7-8].

## B. Oral inhaled products

The success of an orally inhaled product is a combination of the device, the formulation and the patient's technique[9]. As with oral formulations, development starts in the laboratory and the performance of prototypes is measured via particle size distribution (PSD) testing. While attempts continue to use PSD profiles as a predictor of in vivo deposition, the reality is that there is no direct correlation between individual or grouped stages and the anatomy of the lungs[10]. Consequently, while comparable in vitro performance can be used to support claims of equivalence, de novo data cannot be relied upon to predict lung deposition. Products for oral inhalation can be radiolabelled by the addition of a radionuclide (eg 99mTc) to the formulation. In vitro testing is performed to confirm that the PSD of the radiolabel and the drug matches, ensuring that the deposition pattern of the radiolabel is representative of the drug molecule[11]. Scintigraphic data are most commonly used to quantify the initial deposition pattern providing a measure of how efficiently the device delivers the formulation, to which anatomical regions and the extent of lung penetration.

## C. Nasal products

Nasal administration is used for delivery to the systemic circulation (large surface area, non-invasive delivery) or for local delivery[12]. Delivery via the nasal cavity has been explored to deliver drug to the sinuses, and also to the olfactory region to achieve delivery to the brain. Consequently, drug products are often designed to target delivery to specific regions of the nasal cavity. Scintigraphic images co-registered with an MRI scan of the head can be used to quantify the amount of drug formulation delivered to target sites. Specific anatomical regions can be identified, or the cavity can be divided into zones such as upper:lower:inner:outer[13]. Further, scintigraphic imaging can provide evidence to support statements to the regulators that nasal delivery results in no deposition to the lungs.

## D. Locally acting drug molecules

The quantification of the availability of the active moiety at the site of action, ie the measurement of bioavailability, is a fundamental element of pharmaceutical development. For molecules which reach their site of action via the systemic circulation, pharmacokinetic parameters are an accepted surrogate measure and these data underpin the majority of safety, efficacy and bioequivalence assessments. However, for molecules that do not rely on systemic availability, this raft of assessments can be challenging to complete.

Bioavailability may be assessed by 'measurements intended to reflect the rate and extent to which the API becomes available at the site of action'[14,15]. Traditionally, for locally acting drugs these measurements have been limited to pharmacodynamic assessments, and large clinical trials to confirm efficacy.

For locally acting molecules delivered via the oral inhaled route, the use of in vitro assessments and the quantification of lung deposition via imaging are already recognised as supporting data – although pharmacokinetic data are still deemed to be advantageous[16,17]. The regulators now also recognise that the use of comparative clinical trials is inefficient and prohibitively expensive for locally acting molecules delivered to the gastrointestinal tract. As part of the FDA Critical Path Initiative, in vivo imaging has been suggested as a method to directly assess the rate of drug release at the target site[18]. Scintigraphic data provides a measure of both the location and rate of drug release, and comparative assessments of innovator versus test product can be performed.

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